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CC/NUMBERS 51-52
DECEMBER 19-26, 1988

Weirich G, Wren J & Siddall J B. Developmental changes of the juvenile hormone esterase activity in haemolymph of the tobacco hornworm, *Manduca sexta*. *Insect Biochem.* 3:397-407, 1973.
[Zoecon Research Laboratory, Palo Alto, CA]

Juvenile hormone esterase activity showed peaks at specific times during development that were unrelated to fluctuations of general (α-naphthyl acetate) esterase activity. These observations suggested a role for juvenile hormone esterase in the regulation of juvenile hormone titers in insects. [The SCI® indicates that this paper has been cited in over 105 publications, making it this journal's most-cited paper.]

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October 7, 1988

In 1970 I came from Germany to Palo Alto to join a multinational team of chemists, biochemists, and physiologists at the Zoecon Research Laboratory dedicated to an interdisciplinary exploration of juvenile hormone (JH). The company was founded on the premise of finding novel, specific, and environmentally harmless agents for insect control based on a better understanding of the physiology and biochemistry of JH. Jean Wren had just returned to California after several years in England and was ready to apply her expertise in the biochemistry of vertebrate steroid hormones to a new mission. With the encouragement of the late John Siddall, then director of research at Zoecon, we embarked on a study of the enzyme(s) responsible for the *in vitro* JH hydrolysis in the *Manduca sexta* hemolymph.

Michael Slade and Charles H. Zibitt were engaged in an extensive investigation of JH metabolism in *M. sexta* in the same lab and had found that hydrolysis of the ester moiety was a major reaction in this species and that it occurred in hemolymph and various tissues.[1] This was a very puzzling and unusual finding: a hormone that was broken down and inactivated in the medium supposed to transport it to its target tissues. Was this an artifact or a function of the omnipresent, unspecific esterases without physiological relevance? Was the enzyme present at all times? Was the hormone, when released from the corpora allata, perhaps protected in some way? All these questions caused considerable excitement, when we set out for our investigation of what became known as JH esterase.

Our finding that the JH esterase activity in hemolymph showed peaks of activity at specific times during development suggested a role in the control of the JH titer. Unfortunately, it turned out that Zoecon was not able to support the basic research effort at the breadth at which it had originally started, and our collaboration came to an unexpected and abrupt end before this paper appeared in print.

Today, after 15 years of intensive research in many laboratories, the exact nature of the role of JH esterase in hemolymph has not yet been established conclusively.[2,3] However, our knowledge of JH esterase has been broadened by studies involving many species,[2] and it has advanced to state-of-the-art enzyme biochemistry.[3] The metabolic relationship between JH and JH acid has turned out to be more complex than anticipated in the early studies. At certain stages in the development of some insect species, the corpora allata release JH acid[4] instead of JH, and JH acid in hemolymph can be a precursor of JH[4,5] as well as its inactivation product.

Our report was the first one dealing specifically with JH esterase. At that time nobody could have foreseen the proliferation of JH esterase research. The great activity in this area has certainly been a major reason for the emergence of our paper as a *Citation Classic*. We had the good fortune to be in the right place at the right time.

1. **Slade M & Zibitt C H.** *Metabolism of cecropia juvenile hormone in insects and in mammals*. (Menn J J & Beroza M, eds.) *Insect juvenile hormones: chemistry and action*. New York: Academic Press, 1972. p. 155-76. (Cited 115 times.)
2. **Hammock B D.** Regulation of juvenile hormone titer: degradation. (Kerkut G A & Gilbert L I, eds.) *Comprehensive insect physiology, biochemistry and pharmacology*. Oxford, England: Pergamon Press, 1985. Vol. 7. p. 431-72. (Cited 20 times.)
3. **Abdel-Aal Y A I & Hammock B D.** Apparent multiple catalytic sites involved in the ester hydrolysis of juvenile hormones by the hemolymph and by an affinity-purified esterase from *Manduca sexta* Johannson (Lepidoptera: Sphingidae). *Arch. Biochem. Biophys.* 243:206-19, 1985. (Cited 5 times.)
4. **Bhaskaran G, Sparagana S P, Dahm K H, Barrera P & Peck K.** Sexual dimorphism in juvenile hormone synthesis by corpora allata and in juvenile hormone acid methyltransferase activity in corpora allata and accessory sex glands of some lepidoptera. *Int. J. Inver. Reprod. Devel.* 13:87-100, 1988.
5. **Weirich G F & Culver M G.** S-adenosylmethionine: juvenile hormone acid methyltransferase in male accessory reproductive glands of *Hyalophora cecropia* (L.). *Arch. Biochem. Biophys.* 198:175-81, 1979. (Cited 15 times.)